Beta Cell Failure in Diabetics

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Abstract: *Beta cells (beta-cells, β-cells) are a type of cell in the pancreas located in the islets of Langerhans. They make up 65-80% of the cells in the islets.the primary function of a beta cell is to store and release insulin. Insulin is a hormone that brings about effects which reduce blood glucose concentration. Beta cells can respond quickly to spikes in blood glucose concentrations by secreting some of its stored insulin while simultaneously producing more.Any dysfunction in d beta cell present in d islets of langerhans leads to diabetics*

Keywords: beta cell, diabetes, failure, biochemistry, young age, insulin

1. Introduction

Diabetes is characterized by high blood glucose levels as a result of insufficient insulin for the body's needs. It is a hetero- geneous disorder with multiple etiologies. Type 1 diabetes (T1DM) is an autoimmune disease that results in b cell destruction. It usually presents in childhood, accounts for 5%–10% of all diabetes, and is associated with the presence of islet-cell antibodies, and patients require lifelong insulin; it will not be considered further here. Type 2 diabetes (T2DM), the most common form of the disease, is influenced by lifestyle factors, such as age, pregnancy, and obesity, but has a strong genetic component. Multiple genes are thought to be involved, each producing a small effect on T2DM risk. An increasing number of rare monogenic forms of diabetes that result from mutations in a single gene have also been identified. They amount to 1%–2% of all diabetes in Europe, and almost all are characterized by reduced insulin secretion. Accumulating evidence also implicates impaired insulin release in T2DM.(1,2)

The last decade has seen an explosion of new information about the mechanism of insulin secretion and the genetic causes of diabetes, emphasizing the importance of impaired b cell function in both polygenic and monogenic disease. This Review focuses on these recent findings.

2. Glucose Transport

B Exocytosis of insulin granules requires an increase in intracellular calcium that (at least in the case of glucose-induced insulin secretion) results almost entirely from calcium influx through plasmalemmal voltage-gated calcium channels Their opening is controlled by the ATP-sensitive potassium (KATP) channel, which plays a pivotal role in insulin secretion by linking cell metabolism to the membrane potential. At low plasma glucose levels, this channel is open and K+ efflux through the open pore keeps the membrane hyperpolarized, preventing electrical activity, calcium channel opening, calcium influx, and insulin secretion. An increase in plasma glucose leads to increased glucose uptake and metabolism by the b cell and thus to a rise in metabolically generated ATP and a concomitant fall in MgADP. These changes in adenine nucleotide concentrations close KATP channels, thereby initiating electrical activity, calcium influx, and insulin secretion. Sulphonylurea drugs, such as glibenclamide, also stimulate insulin secretion by closing KATP channels, but they do so by binding directly to the channel, thus bypassing the metabolic steps. These drugs have been used for almost 60 years to treat T2DM and, more recently, certain monogenic forms of diabetes.(2,3,4)

Glucose metabolism also has effects downstream of KATP-channel closure and calcium influx that result in amplification of insulin secretion. The details of the mechanism are still not fully understood, but the end result is an increase in the release probability of the secretory granules. (12)Glucose is almost unique among nutrients in that it has the capacity to initiate insulin secretion. Other fuels such as amino acids and fatty acids enhance glucose-induced insulin secretion but generally have little stimulatory effect on their own. As a consequence, insulin secretion is dependent on glucose metabolism. Hormones and neurotransmitters also modulate insulin secretion, primarily by influencing the release competence of the insulin granules without elevating intracellular calcium. Current interest is focused on glucagon-like peptide-1 (GLP-1), which is released from gut L cells in response to the presence of glucose and other nutrients in the gut lumen and potentiates insulin secretion. It stimulates b cell production of intracellular cAMP, which Stimulus-Secretion Coupling in Human b Cells (A) Glucose is taken up via the glucose transporter Glut1 and phosphorylated by glucokinase (GCK). Further metabolism, especially in the mitochondria, results in generation of ATP at the expense of ADP. This leads to KATP-channel closure. Sulphonylureas (SU) inhibit the channel by direct binding, bypassing metabolism. The increased membrane resistance (Rm[) resulting from KATP-channel closure allows small background inward currents, such as those associated with spontaneous opening of T type Ca2+ channels to depolarize the b cell (JY). This leads to regenerative activation of voltage-gated L type and P/Q type Ca2+ channels and Na+ channels, which produces action potential firing. The associated Ca2+ influx triggers exocytosis of insulin granules (SG). In- cretins such as GLP-1 potentiate exocytosis by both protein kinase A (PKA)-dependent and Epac2-dependent mechanisms. Plus signs indicate stimulation, and minus signs inhibition, of the indicated process(es). PM, plasmalemma. (B) Ca2+-channel clustering and extent of [Ca2+]i domains before and after long-term FFA expo- sure. SG, secretory granules.acts by PKA-dependent and PKA-independent mechanisms to amplify granule exocytosis, as well as by enhancing KATP-channel closure, b cell electrical activity, and calcium release from intra- cellular stores (reviewed in Leech et al.,

2011). Most of these effects manifest only at elevated plasma glucose levels, thus accounting for the glucose dependence of GLP-1-potentiated insulin secretion. Release of incretin hormones in the gut, such as GLP-1 and GIP, explains why an oral glucose challenge produces a much larger stimulation of insulin secretion than an intravenous glucose challenge.(4,5,6,7,16)

3. Beta Cell Dysfunction and Insulin Resistance

Beta cell dysfunction and insulin resistance are inherently complex with their interrelation for triggering the pathogenesis of diabetes also somewhat undefined. Both pathogenic states induce hyperglycemia and therefore increase insulin demand. Beta cell dysfunction results from inadequate glucose sensing to stimulate insulin secretion therefore elevated glucose concentrations prevail. Persistently elevated glucose concentrations above the physiological range result in the manifestation of hyperglycemia. With systemic insulin resistance, insulin signalling within glucose recipient tissues is defective therefore hyperglycemia perseveres. Beta cell dysfunction supersedes insulin resistance in inducing diabetes. Both pathological states influence each other and presumably synergistically exacerbate diabetes. Preserving beta cell function and insulin signalling in beta cells and insulin signalling in the glucose recipient tissues will maintain glucose homeostasis.(8,9,10,15)

Pathogenesis
#Type 1 diabetes mellitus, also known as insulin dependent diabetes, is believed to be caused by an autoimmune response where the body's own immune system attacks the beta cells and destroys them. This means the body can no longer produce and secrete insulin into the blood and regulate the blood glucose concentration.

#Type 2 diabetes mellitus, also known as non insulin dependent diabetes, is caused by many factors including: age; family history; obesity and consuming a diet high in simple sugars. The beta cells, however, can still secrete insulin but the body has developed a resistance and its response to insulin has declined. It is believed to be due to the decline of specific receptors on the surface of the liver and muscle cells which lose their ability to respond to insulin that circulates in the blood.[17](18)

#Insulinoma is a rare tumor derived the neoplasia of beta cells. Insulinomas are usually benign, but may be medically significant and even life-threatening due to recurrent and prolonged attacks of hypoglycemia.

Young Age Diabetics
Familial young-onset diabetes is typically diagnosed outside the neonatal period but before 25 years of age. Mutations in the glucokinase and HNF1A genes account for about 70% of cases. Heterozygous loss-of-function mutations in the glucokinase gene (GCK) lead to lifelong, mild, stable fasting hyperglycemia from birth. However, this is often only detected later in life, such as during routine screening in pregnancy (Osbak et al., 2009). GCK mutations act by decreasing glucose-dependent ATP production, which results in impaired KATP closure and reduced insulin secretion. Treatment is rarely needed and ≥85% of patients can be managed by diet alone. Microvascular complications are also rare, reflecting the fact that glucose homeostasis is not severely impaired.

Five genes associated with familial young-onset diabetes are transcription factors that interact in a complex network to regulate gene transcription. They are needed both for correct functioning of adult b cells and for b cell development. The most common mutations are found in the homeobox genes HNF1A and HNF4A; mutations in HNF1B, IPF1, and NEUROD1 are more rare. Most mutations cause a loss of function and are inherited in an autosomal-dominant manner. They lead to a progressive deterioration of b cell function, increasing hyper- glycemia, and eventual diabetes. Studies of mouse models suggest that the impaired insulin secretion may be a result of defective metabolism (Dukes et al., 1998). Whereas heterozy- gous mutations cause a phenotype that is largely confined to the b cell, homozygous mutations in these transcription factors cause a range of additional effects, reflecting the role of these proteins in extra pancreatic tissues.(11,12,13,14)

4. Conclusion

Though there is a strong genetic predisposition to diabetes,The massive increase of its incidence in recent years is not due to genetic changes but is due tothe rise in obesity. It is clear that weight control is highly beneficial in T2DM, and recent studies show that it is even possible to reverse established disease by bariatric surgery and caloric restriction ,beta cell failure is a complication seen in T2DM and not the cause for the onset of disease.further research on the topic is required to have a better understanding of the disease and its complications since there is a drastic increase in the incidents of diabetes in the past 2 decade which might be primarily due to life style and food habits and hence young adults are predisposed to diabetes at a very early age. Importance of life style modification along with good eating habits can aid with weight loss and hence help to control T2DM which occurs in obese individuals.

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